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ORIGINAL RESEARCH ARTICLE

Design and Evaluation of Fast Disintegrating Tablets of Metformin by Effervescence Method

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ABSTRACT:

The objective of the present study was to develop simple fast disintegrating tablets of Metformin for improving patient compliance, especially paediatric and geriatric categories by effervescent method. Croscarmellose sodium was used as superdisintigrant along with blend of sodium bicarbonate, tartaric acid and anhydrous citric acid in different ratios as effervescent material and directly compressible mannitol to enhance the mouth feel. The prepared batches of tablets were evaluated for weight variation, friability, hardness, drug content uniformity, in-vitro dispersion time. The tablet formulation containing 10% w/w of Crospovidone, 20% w/w sodium bicarbonate, 15%w/w citric acid and 20%w/w of MCC emerged as the overall best formulation (with an in vitro dispersion time of approximately 18s, t50%=1.23 min and t70%=1.57 min), based on the in-vitro drug release characteristics, compared to commercial conventional tablet formulation (which shows 118s, 14.09 min and 23.48 min respectively). Infrared spectroscopic studies revealed no drug–excipient interactions. Short-term stability studies conducted at 40 ±2°C/75±5%RH on the best formulation indicated that there were no significant changes in drug content. The present study clearly demonstrates that fast dissolving tablets of Metformin could be successfully prepared by direct compression method in a cost effective manner.

Key words: Crospovidone, Fast Disintegrating Tablets, Effervescent method.

INTRODUCTION

Since the last two decades, there has been an increase in demand for more patient compliant dosage forms. As the development cost of a new chemical entity is very high, the pharmaceutical companies are now more focused on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects [1].

Dysphagia (Difficulty in swallowing) is a common problem for age groups, especially the elderly and pediatrics, because of physiological changes associated with those groups [2,3,4].Other categories that experience problems include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack. Sometimes it becomes difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called mouth dissolving tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water.

The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets and rapimelts. However, of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as orodispersible tablets. Recently, European Pharmacopoeia has used the term “orodispersible tablet” for tablets that disperse readily and within three minutes before swallowing [5]. Upon ingestion, the saliva serves to disperse/dissolve the dosage form; the saliva containing the dissolved/dispersed medicament is then swallowed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In these cases, the bioavailabilities of drugs are significantly greater than those observed from conventional solid forms such as tablets and capsules [6]. In the present study, orodispersible tablets of Metformin (an antidiabetic) [7], were designed using directly compressible excipient

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with the prime objective of arriving at a cost effective product. The designed tablets were evaluated for hardness, friability, weight variation, in vitro dispersion time, drug content uniformity, in vitro dissolution rate (in pH 6.8 phosphate buffer) and short term stability.

MATERIALS AND METHODS

Materials: Metformin was received as a gift sample from Aurobindo Pharma Ltd. (Argus). Croscarmellose sodium, Tartaric acid, Pearlitol SD-200, Aspartame and purified talc IP were obtained as gift samples from Colorcon Asia Pvt Ltd, Goa**.** All the other chemicals used were of analytical reagent grade.

Preparation of Fast Dissolving Tablets by Direct Compression Method [8]:

Fast disintegrating tablets of Metformin were prepared by direct compression method according to the formulae given in (**Table 1**). All the ingredients (except purified talc) were accurately weighed and sifted through #44 mesh separately. Sodium bicarbonate and anhydrous citric acid were pre-heated at a temperature of 80° to remove absorbed moisture and were thoroughly mixed in a mortar to get a uniform powder and then added to other ingredients. The ingredients after sifting through sieve No. 44 were thoroughly mixed by geometrical order. The blend thus obtained was directly compressed into tablets of 150 mg weight (at ambient temperature and humidity conditions) on rotary tablet punching machine using 8 mm round flat punches.

EVALUATION:

In order to determine the weight variation twenty tablets were selected at random and weighed individually using Shimadzu digital balance. The individual weights were compared with the average weight for determination of weight variation [9]. Hardness and friability of the tablets were determined[10] by using Monsanto Hardness Tester (Pharmalab, Ahmedabad, India) and Roche Friabilator (Pharmalab, Ahmedabad, India) respectively. Preweighed tablets were placed in a plastic chamber attached to a motor revolving at a speed of 20 rpm for 5 minutes. The tablets were then dusted, reweighed and the percentage weight loss was calculated [11]. Ten tablets from each formulation were selected randomly and their thickness was measured using a screw gauge in order to calculate the thickness variation.

For content uniformity test, ten tablets were weighed and pulverized to a fine powder. The powder equivalent to 50 mg of drug was extracted in to distilled water, and the solution was filtered through a 0.22µ membrane filter and measuring the absorbance. (UV-Visible Spectrophotometer, Shimadzu 1700) after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was determined as an average of three determinations [12].

The in-vitro dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5º C and the time required for complete dispersion was determined. [13] All the evaluations results are represented in (**Table 2**)

In-vitro dissolution[14] of the fast disintegrating tablet and conventional commercial tablets were studied in USP XXIII type-II dissolution test apparatus (Electrolab, model: TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37+0.5°C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5ml) were withdrawn at specified intervals of time and replaced with fresh medium and analyzed for drug content by measuring the respective absorbance. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent of the drug released and represented in (**Table 3**).

Stability Testing:

Short-term stability (accelerated) studies was carried out by storing the tablets at 40°C±2°C/ 75±5% RH over a 3 month period in an amber coloured rubber stoppered vial. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and in vitro dispersion time and the results were subjected to statistical analysis using student‘t’ test.

RESULTS AND DISCUSSION

Fast disintegrating tablets of Metformin were prepared by effervescent method employing Croscarmellose sodium as super-disintegrant along with blend of sodium bicarbonate, anhydrous citric acid and tartaric acid in different ratios. Directly compressible mannitol (Pearlitol SD 200) was used as to enhance mouth feel. A total of twelve formulations were designed. As the blends were free flowing (Angle of repose<30°, and Carr’s Index <15%) tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below ±7.5%. Drug content was found to be in the range of 98.72 to 101.08 %, which in within acceptable limits. Hardness of the tablets was found to be 2.5 to 2.95 kg/cm and friability below 1% was an indication of good mechanical

resistance of the tablets. Among all the designed formulations, two formulations, viz., ECP_4 and $ECCS_4$ were found to be promising and displayed an in vitro dispersion time ranging from 18 to 34seconds, which facilitates their faster dispersion in the mouth.

Overall, the formulation ECP_4 containing 10% w/w of Crospovidone along with blend of 20%w/w sodium bicarbonate, 15%w/w anhydrous citric acid and 20%w/w of microcrystalline cellulose of was found to be promising and has shown an in vitro dispersion time of 18s, when compared to control formulation (EC_0) which shows 59s.

In-vitro dissolution studies on the promising formulations (ECP_4 and $ECCS_4$), the control (EC_0) and Commercial Formulation (ALNAMET-SR 500 mg, Alna Biotech, Chandigarh, India) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5, 10 and 15 min (D_5, D_{10} and D_{15}), $t_{50\%}$, $t_{70\%}$ and t_{90}. This data reveals that overall, the formulation ECP_4 containing 10% w/w of Crospovidone along with effervescent mixture has shown nearly eleven-fold faster drug release ($t_{50\%}$ 1.24 min) when compared to the CF of Metformin ($t_{50\%}$ 14.09 min) and released five-times more drug than the control formulation in 10 min.

Short-term stability studies of the above formulations indicated that there were no significant changes in drug content and in vitro dispersion time at the end of 3 months period ($P<0.05$).

Table 1: Composition of different formulations of fast disintegrating tablets of Metformin

Ingredients (mg/tablet)	Formulation Code												
	Eo	**EP_2**	**EP_4**	**EP_6**	**EP_8**	**ES_2**	**ES_4**	**ES_6**	**ES_8**	**ECC_2**	**ECC_4**	**ECP_2**	**ECP_4**
Metformin	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Sodium bicarbonate	18	18	18	18	18	18	18	18	18	18	18	18	18
Tartaric acid	18	18	18	18	18	18	18	18	18	18	18	18	18
Pregelatinized starch	-	3	6	9	12	-	-	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	3	6	9	12	-	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	-	-	-	3	6	-	-
Crospovidone	-	-	-	-	-	-	-	-	-	-	-	3	6
Microcrystalline cellulose	30	30	30	30	30	30	30	30	30	30	30	30	30
Aspartame	6	6	6	6	6	6	6	6	6	6	6	6	6
Flavour	3	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Purified talc IP	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Pearlitol SD-200	60.25	57.25	54.25	51.25	48.25	57.25	54.25	51.25	48.25	57.25	54.25	57.25	54.25
Total Weight	150	150	150	150	150	150	150	150	150	150	150	150	150

Table 2: Evaluation of fast disintegrating tablets of Metformin

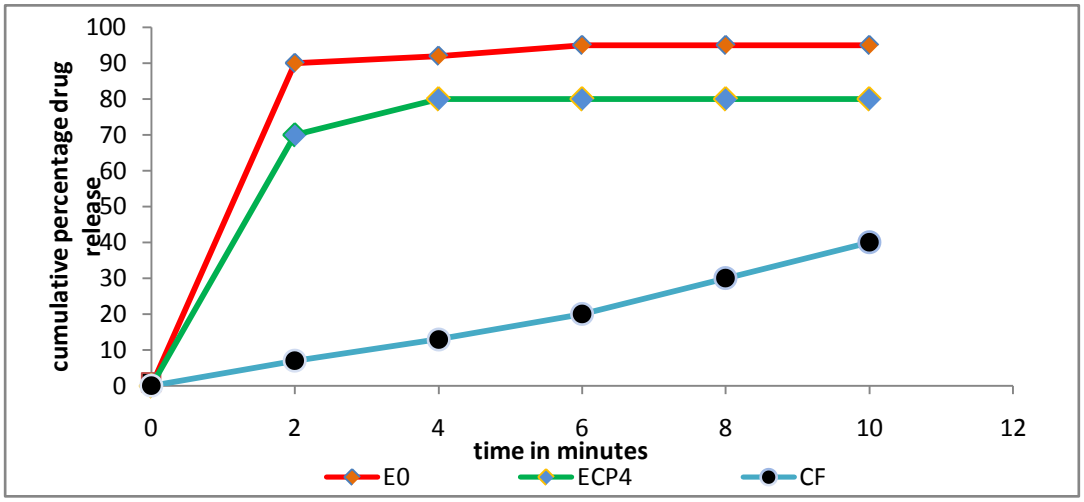
Formulations	Average weight*(mg) ± SD	Hardness* (kg/cm^2)± SD	Friability (%)	Thickness* (mm)	Percent Drug content*± SD	*In vitro* Dispersion time*(s) ± SD
E_0	148±0.002	2.81±0.02	1.19	2.59±0.06	98.37±1.20	58.41±0.23
EP_2	151±0.002	2.73±0.01	0.84	2.85±0.05	99.87±1.77	51.09±2.88
EP_4	147±0.002	2.54±0.02	0.97	2.67±0.02	100.04±0.16	41.78±5.50
EP_6	152±0.001	2.91±0.03	0.94	2.48±0.09	97.52±1.53	53.13±4.58
EP_8	148±0.001	2.78±0.05	0.88	2.78±0.07	100.54±0.25	50.89±1.55
ES_2	148±0.002	2.76±0.01	0.95	2.55±0.02	98.18±0.68	41.47±1.00
ES_4	151±0.002	2.86±0.04	0.91	2.83±0.02	99.44±1.99	34.98±0.58
ES_6	149±0.001	2.84±0.12	1.08	2.58±0.03	100.25±0.57	53.49±1.15
ES_8	150±0.002	2.76±0.02	0.91	2.77±0.10	98.44±1.12	51.28±6.11
ECC_2	148±0.002	2.78±0.04	0.87	2.71±0.05	101.56±0.01	38.39±2.51
ECC_4	149±0.001	2.93±0.01	0.96	2.75±0.04	100.18±0.63	39.47±1.39
ECP_2	147±0.002	2.58±0.03	1.11	2.67±0.02	98.79±1.94	52.91±2.00
ECP_4	152±0.001	2.83±0.02	0.97	2.73±0.77	99.85±1.07	18.13±1.47

Table 3: In-vitro dissolution parameters of different formulations in pH 6.8 phosphate buffer

Formulation Code	$t_{50\%}$ (min)	$t_{70\%}$ (min)
E_o	1.50	1.94
ES_4	1.22	1.73
ECC_2	1.25	1.81
ECP_4	1.23	1.57
CF	14.09	23.48

CF= conventional commercial formulation, $t_{50\%}$ = time for 50% drug dissolution, $t_{70\%}$ = time for 70% drug dissolution

Fig 1: Comparative cumulative percent drug release Vs time plots of control (E_0), promising (ECP_4) and commercial conventional tablet formulation (CF) in pH 6.8 phosphate buffer



CONCLUSION

The present study conclusively indicates that formulation ECP_4 is very much promising as fast dissolving (fast disintegrating) tablet formulation of Metformin with an in vitro dispersion time of 18s. Effervescent technique would be an effective approach compared with the use of more expensive adjuvants in the formulation of fast disintegrating tablets with improved drug dissolution, patient compliance, convenience and acceptability.

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