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Research article

Formulation development and evaluation of Ambroxol HCL paper tablet

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Abstract

The possibility to compress ordinary paper into tablets was systematically investigated in this study The SmartFilm®-technology is a novel approach to overcome poor solubility. The technique uses commercial paper in which API can be loaded in amorphous state, thus increasing dissolution rate dc/dt and solubility cs when compared to bulk material. Results proved that tablets can be made from paper, independent of the type of paper used. The tablets appear shiny and with a smooth surface. The pharmaceutical quality was acceptable, i.e., all tablets fulfilled the requirements for tablets according to the Pharmacopeia. The average of drug content was found to be 102.21±2, 101.15±5, 102.10±3, 56.1±7 respectively from F1 to F4. Batch F1 to F4 showed drug release 97.8%, 92.04%, 79.72%, 72.72% respectively.

Introduction

Oral administration has been considered as one of the most compatible drug delivery routes because of ease of administration, patient compliance, adjusted dose, flexibility in the design of dosage form [1]. Oral administration is not only employed for local but also for systemic delivery of most of drug molecules, including micro molecule drugs to macromolecule [2]. An oral drug delivery system has said to be ideal drug delivery system when it could be delivered the drug to a biological target at adequate concentrations with optimal dosage windows [3]. It doesn't require smart sterile facilities, there is no direct involvement of health care professionals and dosage manner is flexible [4]. It is fact that the oral route is one of the most compatible way for administration of any new active molecule [5]. Oral drug delivery is said to be successful when the active pharmaceutical ingredient (API) can be successfully released from the oral dosage form and can completely dissolve in the body fluid, because only dissolved API can be taken up from the body. Unfortunately, now a days various new chemical entities (NCE) possess low solubility [6]. For the low water-soluble drugs with low membrane permeability, which comes under BCS class IV, formulation strategies can do little modifications to improve their absorption due to the low membrane permeability. Proper formulation is importance aspect to establish a successful orally administered product. [7]. A newly developed method uses common paper as matrix and loads active drug moieties in amorphous state into the pores of the paper so, it also called smart Film®-technology as the paper loaded with an active pharmaceutical ingredient hence called smart Films which can then be transferred into hard capsules or if more loading capacities are required as single dosages, the films can further be transferred into tablets [8]. The model technology is simple and thus a highly promising and better plan for the successful oral dosage form of poorly soluble APIs. But, oral administration of paper might not be very comfortable for the consumer or patient. Hence, the compression of smart Films® into comfortable oral dosage forms is needed to improve the acceptance criteria of the novel technology. First option is the filling of the paper into hard capsules. As larger amounts of paper cannot be filled into the capsules hence, a dosage form that can be used for larger amounts of smart Films® is a better option for a successful application of smart Films® in the future. Initial results already demonstrate that paper can be compressed into tablets without addition of any further excipients [9, 10]. A systematic study inspects the possibility to compress different kinds of paper and/or drug-loaded paper into tablets was not still performed and nothing is known about the pharmaceutical properties of such tablets. Therefore, the aim

of this study was to transform different types of drug-loaded paper into tablets and to characterize their pharmaceutical properties, e.g., hardness, friability, disintegration and their suitability for oral administration.

Materials and Methods

Production of paper tablets

The method adopted for producing paper tablet of Ambroxol HCl summarized in figure 1. Composition of various batches is shown in table 1. Firstly, paper was cut into sheets with a mass of about 600 to 900 mg for this the density of the paper was roughly determined by analysing the height and the respective mass/volume. The sheets were loaded with an aqueous solution of Ambroxol HCl (25mg/mL) by adding 250 µL of the solution to the piece of paper with a pipette. Then allow to dry. After drying the procedure was repeated again, leading to a total load of 50 mg of Ambroxol HCl per sheet of paper. The sheet was cut into small pieces (each about 1 cm× 1 cm). The drug-loaded pieces of paper were again manually placed into the cavity of the tablet press and manually compressed. The properties of the drug-loaded tablets were investigated according to the European Pharmacopeia.

Characterization of the tablets [11, 12]

Thickness

Ten tablets from each formulation of Ambroxol HCl paper tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using Vernier Callipers and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.

Tablet Hardness

Hardness of all the formulations of Ambroxol HCl paper tablets were measured by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten tablets with known weights were recorded in kg/cm2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 4-5 Kg for tablet is considered as acceptable limit.

Friability

Previously weighed ten Ambroxol HCl paper tablets from each batch were taken in Roche friabilator (Roche friabilator, Secor India). After100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust using a soft muslin cloth and the total remaining weight was recorded. Friability was calculated from the following formula. (Equation 1)

$$\%F = \frac{wi - wf}{wi} \times 100$$

Where Wi and Wf were the initial and final weight of the tablets before and after friability test. For any compressed tablet that the lose less than 0.1 to 0.5% and maximum up to 1% of the tablet weigh are consider acceptable.

Table 1. Composition of various batches.

Ingredients	F1	F2	F3	F4
Ambroxol hcl	50mg	50mg	50mg	50mg
Coffee filter paper	605mg			
Kitchen roll paper		605mg		
Whatman Filter paper			640 mg	
Envelop paper				865 mg
Total	655 mg	655 mg	690 mg	915 mg

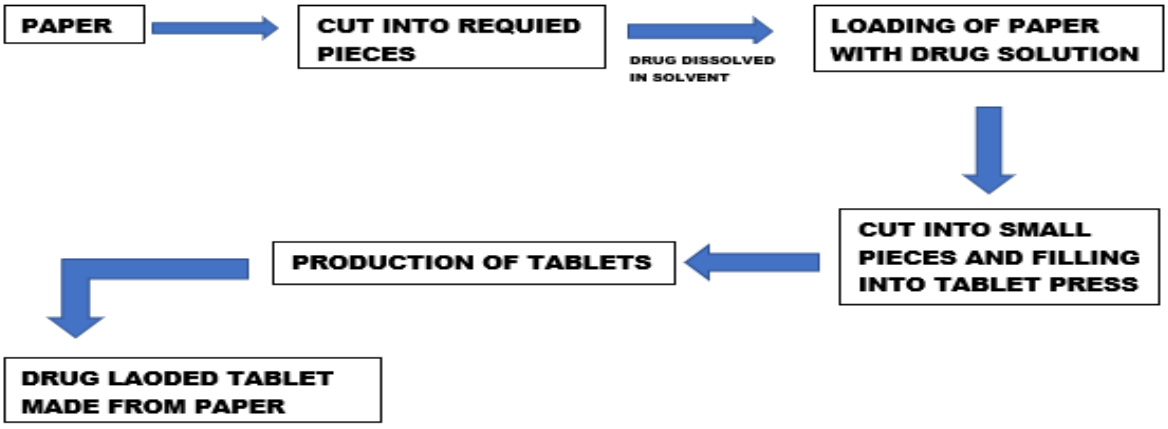

Figure 1. Steps involve in production of paper tablet.

Weight variation test

All formulated Ambroxol HCl tablets were evaluated for weight variation as per USP monograph. Ten tablets were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130 mg or less is 10% whereas for average weight between 130-324 mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviates from the average weight by not more than 7.5% and no tablet deviates by more than 15%.

Content uniformity

Five Ambroxol HCl paper tablets were taken and triturated to form powder and powder equivalent to dose of drug was taken and dissolved in 100 ml of water & methanol (1:1) The solution was filtered, suitably diluted and the Ambroxol HCl content was measured by using UV Spectrophotometer at 274 nm. Each measurement was carried out in triplicate and the average drug content in each Ambroxol HCl paper tablets was calculated.

Water absorption ratio

A piece of tissue paper folded twice was placed in small Petri dish. (Internal diameter =6.5cm) containing 6ml of water. A tablet was placed on the paper and time required for complete wetting was measured. The wetted tablets were then weighed. Water absorption ratio (R) was determined using following equation

$$R=\frac{Wa-Wb}{wb}\times 100$$

Wa= weight of tablet after absorption

Wb=weight of tablet before absorption

Wetting time

Wetting time is closely related to the inner structure of tablet and to hydrophilicity of excipients. A liner relationship exists between wetting time and disintegration time. Thus, wetting time is important step for disintegration process to takes places. A tablet was placed on the paper and time required for complete wetting was measured.

Disintegration

Disintegration of the paper tablets was investigated after the test method 2.9.1 in water (and in 0.1 M HCl in case of the coated tablets), as described in the European Pharmacopeia 8.0. Tablets (n = 6) were individually placed into the cavities of the disintegration tester (PTZ S, Pharma test, Germany) and time to disintegrate was measured while tablets were moved up and down through a distance of 50 mm to 60 mm (frequency: 29–32 movements/ min, temperature: 37 °C ±2°C). The results were considered as acceptable if tablets were disintegrated within 15 min. Disintegration test for tablet containing excipients also performed with same procedure as performed for paper tablet.

In-vitro dissolution study

The in-vitro dissolution study was conducted for all the formulations using an eight station USP dissolution rate test apparatus type-II. A total volume of 900 ml of phosphate buffer PH 6.8 was taken as dissolution medium, which was maintain at 37°C ± 0.5°C at 50 rpm. 1ml of aliquots was periodically withdrawn and the same volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 10 minutes intervals and after filtering by Whatman filter paper, were analyzed spectrophotometrically at 274nm for determination of ambroxol HCL that were released from m sustained release tablets.

Accelerated stability study

During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. in the present study, stabilities studies were carried out on optimized formulation. The tablet was stored at 40 ± 2°C /75± 5%RH for duration of 45 days, sample was withdrawn and tested for drug entrapment, and drug release study.

Result and Discussion

Density

The density of the paper was roughly determined by analysing the height and the respective mass/volume. Density of various papers such as Kitchen roll paper, Coffee filter paper, Envelop paper and Whatmann filter paper were found to be 64.5, 96.2, 133.3 and 166.6 respectively.

Thickness

Thickness of all formulation batches was found to be 0.4cm. The individual data of all batches are given in table 2.

Hardness

The hardness of all batches was found in the rage of 5.0 to 5.3 kg/cm^2. The details of hardness values are given in table 2.

Friability

The percentage friability was found in the range of 0.1 to 0.57% of all batches. The details of friability are given in table 2.

Weight variation
The weight variation of all formulation batches was found in between 0.2 to 0.38 and details are given in table 2.

Drug content uniformity
To evaluate the tablet potential for their efficacy, the amount of drug in the tablet needs to be monitored from tablet to tablet and batch to batch. The average of drug content was found in range of 56, to 102%. The detail values summarized in table 2.

Water absorption ratio
From the study it was found that the water absorption ratio lies between 31.20 to 39.40and it shown in table 2.

Wetting time
The wetting time was found to be in the range of 35 to 42 seconds. The values shown in table 2.

Disintegration
Disintegration was achieved within less than 60 seconds. Disintegration started with a massive swelling of the tablets within 5 seconds. Within 10 seconds the volume of the tablet was already doubled and tripled after about 20 seconds. After 30 seconds the tablet was disintegrated, i.e., all paper was moist and soft. A full disintegration of the individual small pieces of paper was also achieved after about 1 min to 3 minutes. It is shown in table 2.

In-vitro dissolution studies
The dissolution rate was studied using 900 ml phosphate buffer 6.8 for 77 minutes under sink condition using USP dissolution apparatus. The theoretical drug release profile calculation is important to evaluate the formulation with respect to release rate. The release revealed that the release profile of paper tablet of Ambroxol HCl shows drug release as given in the table 3. Batch F1 to F4 showed drug release are 97.8%, 92.04%, 79.72%, 72.72% respectively. The variation may be due drug holding capacity of papers and cellulose content of papers. The drug release of all formulation was companied and evaluated. The result show that the formulation F1gives more drug release, was considered as optimized formulation (Figure 2).

Table 2. Post compression evaluation parameters of paper tablet.

Formulation	Thickness (cm) Mean ± SD	Hardness (kg/cm²)	Friability (%)	Weight variation (%) Mean ± SD	Water Absorption Ratio Mean ± SD	Wetting Time (sec) Mean ± SD	Disintegration Time (sec) Mean ±SD	Drug Content (%)
Coffee filter paper	0.4±0.003	5.2± 0.14	0.57±0.03	0.22 ± 3.84	39.20±0.20	35.20±0.05	55.31±0.52	102.21±2
Kitchen roll paper	0.4±0.005	5.1± 0.12	0.4±0.01	0.20 ± 1.7	35.90±0.80	36.49±0.30	60.22±0.80	101.15±5
Envelop paper	0.4±0.012	5.0± 0.08	0.1±0.02	0.38 ± 3.74	33.52±0.65	39.80±0.70	120.32±0.12	102.10±3
Whatman filter paper	0.4±0.001	5.3± 0.04	0.1±0.02	0.3 ± 2.10	31.20±0.12	42.03±0.42	125.60±0.50	56.1±7

Table 3. In-vitro dissolution studies of paper tablets.

Formulation/ Time in minute	Coffee filter paper F1	Kitchen roll paper F2	Envelop paper F3	Whatman filter paper F4
0	0	0	0	0
2	6.16	6.16	6.16	3.16
7	11.08	13.56	12.6	11.5
17	17.26	22.18	20.12	17.76
27	25.06	32.46	25.06	25.06
37	33.28	43.14	33.68	33.28
47	46.84	54.24	43.56	41.80
57	62.46	66.16	54.64	51.36
67	79.72	78.9	66.56	61.64
77	97.8	92.04	79.30	72.72

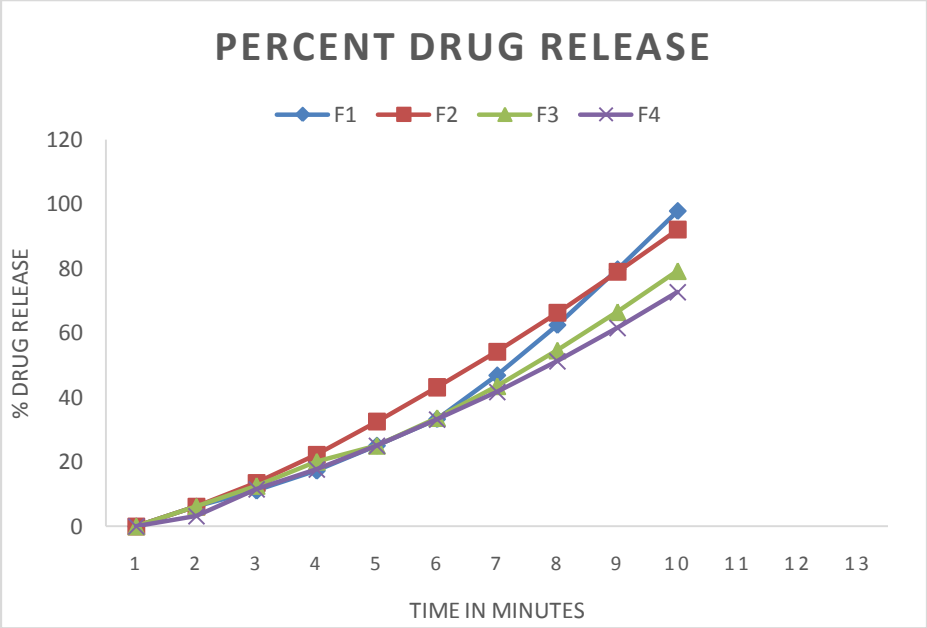

Figure 2. In-vitro dissolution studies of paper tablets.

Table 4. Parameters studies on optimized batch (F1) before and after stability study.

Sr. No.	Parameters	Before	After
1	Hardness	5.2 (kg/cm^2)	5.25 (kg/cm^2)
2	Thickness	0.4cm	0.4cm
3	Friability	0.5% to 0.6%	0.5% to 0.6%
4	Weight variation	0.22% ± 3.84% to 4.4% ± 0.6%	0.23% ± 3.84% to 4.4% ± 0.6%
5	Disintegration	1-3minutes	1-3minutes
6	Drug content	102%	102%
7	Water absorption ratio	39.20±0.20	39.20±0.20
8	Wetting time	35.20±0.05	35.20±0.05

Table 5. Cumulative percent drug release of optimized formulation before and after stability studies.

Time in (min)	Before stability studies	After stability
0	0	0
2	6.16	6.74
7	16.4	16.1
17	27.52	27.3
27	39.4	38.64
37	52.18	52.84
47	65.34	64.43
57	78.9	77.65
67	92.86	93.86
77	97.8	97.5

Evaluation parameter of optimized formulation F1 after stability study

The stability studies were carried out on optimized formulation. The formulation was stored at 40± 20 C/75 ± 5% RH for 45 days. The sample were withdrawn and retested for % drug release studies. It indicates that irrespective of type of paper, these formulations were found to retain their stability for 45 days under the above conditions (Table 4 and 5).

Conclusions

The paper tablet of different papers by using direct compression method the evaluation shows the batches were lies within official standard limit. The paper tablet prepared from coffee filter paper (F1) is assessed fast release of drug, so it can be concluded that the coffee filter paper tablet maintains the fast release as that of other tablet prepared by direct compression.

Above results shows that we can reduce the use of excipients in tablet manufacturing which reduces the cost of tablet and avoid chances of incompatibility.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Authors Contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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