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Original Article

Formulation and Evaluation of Orodispersible Tablets of Ambroxol Hydrochloride

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ABSTRACT

The present study is to design and develop a stable solid oral dosage form of dispersible tablets to deliver with optimum concentration of drug at desired site at specific time comparable to the innovator product with better stability, high production feasibility, and excellent patient compatibility. Formulations were made by wet granulation technique. All the formulations were subjected to physicochemical analysis and out of them Formulation 9 was found to be satisfactory when compared to other formulations. The disintegration time 29.25 sec and percentage of drug release (94.73 %) were found to be satisfactory and it matches with the innovator. So, the batch size was increased in further trial to check the reproducibility (Formulation 9).Finally loaded for stability as per the ICH guidelines.

Keywords: AmbroxolHcl, Sodium starch glycolate NF, Colloidal silicone dioxide, wet granulation technique and drug release studies.

1. INTRODUCTION

A 'patient-friendly dosage form' improves patient acceptance and compliance. Major challenges to this are the bitter taste of drugs and dosage forms that are difficult to ingest, carry or store. Present work explores the potential of ion exchange resins for taste masking of bitter drug, Fexofenadine hydrochloride and formulating it in the form of an Orally Disintegrating Tablet, which is gaining popularity as a dosage form.[1]

Taste masking of bitter drugs is a big challenge to formulator in developing a drug product with good organoleptic properties for patient acceptance and compliance. Though

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there are several methods available for taste masking of bitter actives, a method that is gaining wider acceptance is use of ion exchange resins.[2] However, the utility of ion exchange resins for taste masking is product specific and there are various factors like resin-type, loading method, particle size of resin and degree of cross linking of resin that influence formation of a resinate.[3] Also, in recent times, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the dosage forms developed to facilitate ease of medication, the orally disintegrating tablet (ODT) is one of the most widely employed commercial products.[4] The ODT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. [5]When an ODT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.[6,7]

2. MATERIAL AND METHODS

AmbroxolHCl gifted from Dr. Reddy's laboratories, Amberlite IRP 64 Gift sample Rohm and Haas, Microcrystalline cellulose, Sodium starch glycolate NF, Colloidal silicone dioxide NF, Aspartame, Magnesium Stearate gifted from AR Chemicals.

METHODOLOGY

Method of preparation

Formulation of ambroxol HCL fast dissolving tablets

Ambroxol hydrochloride and amberlite IRP-64 resin were co-sifted through # 40 sieve and used for step-2. Avicel pH101, sodium starch glycolate, aerosil, straw berry flavour and magnesium steriate passed through # 40 sieve and collected in poly bag.[8,9] Ambroxol drug and amberlite IRP-64 resin are dissolved in water and stirred on magnetic stirrer for specific period of time and allowed to complex each other to form a taste masked drug resin complex.[10] Transferred the sifted material from step-1and step-2 into the RMG and mixed for 15 minutes Sifted the dried granules through # 20 sieve and collected the oversized granules separately. Magnesium stearate was sifted through # 60 sieve, added to the step-2 blend and mixed for 5 minutes. Granules prepared from above process are subjected for Tablet making. Tablets were compressed using compression machine with lubricated blend, employing appropriate punch tooling. [11,12] Collect the compressed Tablets in double poly lined bag and proceeded for coating.

Table 1: Formulations Table

Ingredient	**Quantity of ingredients**								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	F-6	**F-7**	**F-8**	**F-9**
Drug: resin complex **(In %)**	Eq.60 mg	Eq.60 mg	Eq.60 mg	Eq.60 mg	Eq.60 mg	Eq.60 mg	Eq.60 mg	Eq.60 mg	**Eq.60 mg**
Avicel PH102	25	23	21	25	23	21	21	21	**21**
SSG	2	4	6	----	----	----	4	2	**3**
CCS	----	----	----	2	4	6	2	4	**3**
Aerosil 200	1	1	1	1	1	1	1	1	**1**
Aspartame	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	**0.25**
Strawberry flavor	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	**0.25**
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	**1.5**
Total	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg

EVALUATION STUDIES [12,13]

Parameters related to Drug Resin Complex

Selection of Resin

In the present work weak cation exchange resin i.e. Amberlite IRP-64 &Amberlite IRP-69 are used for the taste masking of AmbroxolHCl. Weak cationic exchange resins are used here because of weak binding capacity and basic nature of AmbroxolHCl; therefore they were selected for the immediate release taste masking formulation. It was observed that stirring for 5 h is required to achieve drug loading equilibrium, hence all further samples were stirred for 5 hours.

Study of Drug-Resin ratios:

To study the effect of drug-resin ratios on rate and extent of drug loading on resin, three different ratios1:1, 2:1, 3:1 of drug-resin were selected .The experiment was carried out by using Amberlite® IRP-64 by single batch method.

Post compression parameters[14,15,16]

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation were calculated. The test for weight variation is passed only if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage.

Friability

The friability values of the tablets were determined using a Roche friabilator. It is expressed in %.20 tablets were initially weighed (initial weight) and transferred to friabilator. Friabilator was operated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

$$\%\text{Friability} = \frac{\text{Initial weight - final weight}}{\text{Initial weight}} \times 100$$

Hardness test: The crushing strength (kg/cm^2) of tablets was determined by using Monsanto hardness tester.

Drug content:

For determination of drug content three tablets from each formulation were weighed individually, crushed and diluted to 100ml with sufficient amount of PH 7.4. Then aliquot of the filtrate was diluted suitably and analysed spectrophotometrically at 223 nm against blank.

Taste Evaluation:

The taste characteristic of Ambroxol hydrochloride ODT formulations was compared in healthy human volunteers, from whom informed consent was first obtained. The evaluation was based on the extent to which subjects liked the taste of each ODT. Formulations were rated on a scale of 0 through 3. Where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness

In vitro drug release of orally dispersed tablets

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium consisted of 900 ml of phosphate buffer pH 3,The release was performed at 37 ^{0}C ± 0.5 ^{0}C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in to the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at 0, 5, 10, 15, 20, 25 & 30 min time intervals and replaced with fresh medium. The samples were filtered through filter paper and analyzed by UV spectrophotometer at 223 nm.

Dissolution parameters:

Medium: Phosphate buffer pH 3

Volume: 900 ml

Apparatus: Dissolution apparatus type 11 of USP (paddle)

Rotation speed: 50 rpm

Temperature: 37 ±0.5°C

Time intervals: 0, 5, 10, 15, 20, 25 & 30 min

3. RESULTS AND DISCUSSION

Preformulation studies

Flow properties of drug

Table 2: Flow properties of drug material

Parameter	S1	S2	S3	Avg.	Type of Flow
Taped Density (gm/ml)	0.46	0.45	0.465	0.458	Good
Bulk Density (gm/ml)	0.41	0.415	0.42	0.415	
Compressibility Index (%)	10.66	10.56	10.8	10.51	
Hausner ratio	1.19	1.20	1.18	1.19	

Drug & compatibility studies

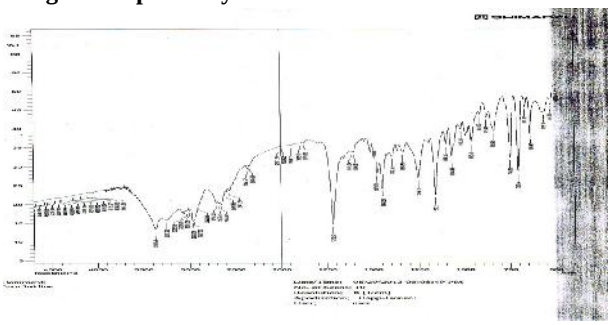

Fig 1: FT-IR Spectrum of Ambroxol hydrochloride

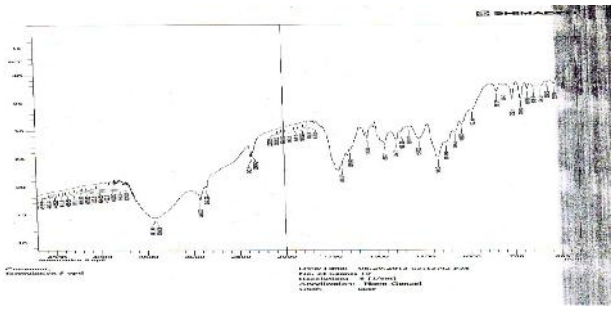

Fig 2: FT-IR Spectrum of Optimized Formulation

Evaluation of pre compression parameters

Table 3: Evaluation of Pre Compression Micromeritic Parameters

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose	Carr's index	Hausner's Ratio
F1	0.44±0.01	0.54±0.044	25.41±0.41	18.51±0.77	1.22±0.52
F2	0.44±0.021	0.55±0.028	27.05±0.21	20.0±0.25	1.25±0.16
F3	0.46±0.014	0.57±0.012	28.19±0.18	19.29±0.16	1.23±0.23
F4	0.45±0.019	0.55±0.023	25.21±0.24	18.18±0.17	1.22±0.14
F5	0.45±0.023	0.54±0.042	24.34±0.43	16.66±0.45	1.20±0.22
F6	0.46±0.015	0.57±0.061	27.20±0.24	19.29±0.57	1.23±0.18
F7	0.45±0.021	0.56±0.034	27.22±0.34	19.64±0.43	1.24±0.21
F8	0.46±0.017	0.56±0.044	28.34±0.32	17.85±0.61	1.21±0.31
F9	0.45±0.012	0.54±0.032	30.18±0.34	16.66±0.62	1.20±0.16

Post compression parameter

Table 4: Evaluation of Post Compression Parameter

Test	Formulations								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**
Weight variation test	90.3	89.8	89.3	90.4	90	90.7	89.3	90.4	90.1
Hardness (Kg/cm^2)	4.2± 0.65	4.1±0. 28	4.4±0. 28	4.2±0. 19	4.3±0. 18	4.5±0. 15	4.5±0. 12	4.7±0. 16	4.8±0. 55
Friability (%)	0.88	0.85	0.82	0.84	0.80	0.79	0.78	0.76	0.72
Drug content (%)	98.23 ± 0.59	97.56 ±0.65	98.28 ±0.35	95.8 ±0.20	98.47 ±0.56	99.90 ±0.10	99.25 ±0.18	95.25 ±0.25	99.25 ±0.15
Wetting time (Seconds)	120.67 ±1 .53	118.33 ±1.15	112.67 ±3.21	108 ±1.00	96.56 ±1.53	96.30 ±2.00	97.25 ±0.18	95.25 ±0.18	95.22 ±0.86
***In vitro* disintegration time (Seconds)**	39.23 ±0.53	45.47 ±0.83	37.81 ±1.23	42.95 ±0.59	38.02 ±1.58	36.24 ±1.11	32.22 ±0.86	36.43 ±0.78	29.25 ±0.95

Table 5: Dissolution Profiles of Ambroxol Hydrochloride Orally Dispersed Tablets Trial Batches

	Cumulative % drug release of formulation F1-F9								
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	**0**
5	32.73	35.95	37.76	29.73	32.97	36.33	38.73	40.53	**42.15**
10	40.03	43.09	47.74	38.01	42.16	45.03	47.32	54.86	**53.35**
15	55.67	58.88	59.23	49.96	53.15	56.67	58.67	63.65	**64.07**
20	63.22	65.61	67.58	58.64	63.96	69.61	71.24	72.31	**76.67**
25	71.46	73.49	75.42	71.52	75.91	78.61	79.92	81.66	**85.16**
30	82.48	84.11	86.54	81.96	83.84	84.78	86.52	87.96	**94.73**

All the values are expressed as mean ± S.D; No. of trails (n) =6

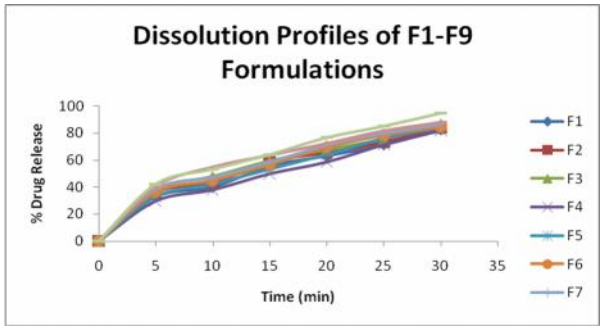

Fig 3: Dissolution profiles of F1-F9 formulations

Table 6: Drug release profiles of innovator and optimized formulation F-9

TIME (min)	% DRUG RELEASE	
	INNOVATOR	F-9
0	0	0
5	55.51	42.15
10	63.7	53.35
15	71.4	64.07
20	81.5	76.67
25	89.2	85.16
30	96.35	94.73

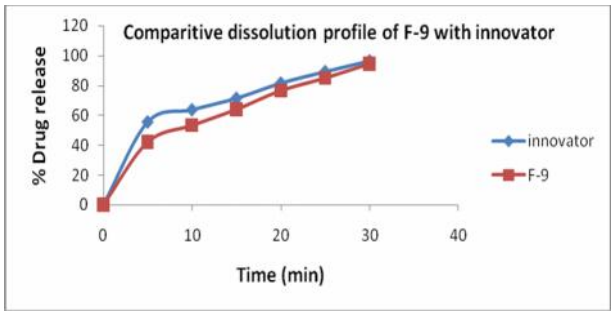

Fig 4: Comparative dissolution profile of F-9 with innovator

Stability Study

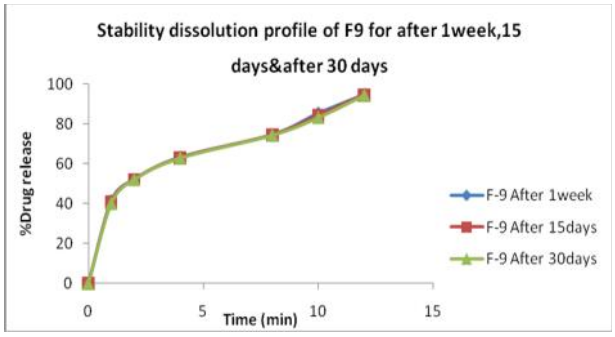

Fig 5: Dissolution profile of optimized batch after stability study

4. SUMMARY AND CONCLUSION

The present study was mainly based upon the "Formulation and evaluation of taste masked orally dispersible tablets of Ambroxol hydrochloride" by direct compression method. Various formulations of Orally Dispersible Tablets of Ambroxol Hydrochloride were prepared by using different proportion & combination of Excipients. Tablet blends were prepared and Micrometric studies were carried out for those blends. Precompressional parameters such as angle of repose, bulk density, tapped density, compressibility index, and Hauser's ratio for physical mixtures of orally dispersible tablet formulations (F1 – F9) were evaluated and the results obtained by UV-Spectroscopy. Formulation (F9) was formulated by including Croscarmellose sodium. The results showed disintegration was within limits and maximum % drug release was found in 30 min .So, formulation (F9) was taken as optimized formulation.

From the results obtained, the *In-vitro* dissolution profile of formula 9 was somewhat better to that of reference product. All the stability results were found to be satisfactory. Hence the designed and developed formula of Ambroxol hydrochloride was stable. Ambroxol hydrochloride Taste masked orally dispersed tablets developed in the present work was found to be pharmaceutically better when compared with innovators product.

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