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Formulation and Evaluation of Reconstitutable Oral Suspension of Ambroxol HCl and Azithromycin

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Abstract: The objective of the present study was to develop dry suspensions for reconstitution like Azithromycin and Ambroxol HCl using powder blends techniques. No commercial product available in combined dosage form. Reconstitutable oral suspension show adequate chemical stability of the drug during shelf life, avoids the physical stability problems. These are dry mixture that requires the addition of water at the time of dispensing. The prepared suspensions were evaluated for flow properties, rheological and sedimentation behavior. The reconstitution oral suspensions of Azithromycin and Ambroxol HCl were found to be stable over its intended shelf life of 15 days after reconstitution. Formulation with Xanthum gum (1.5% and 0.75%) showed excellent sedimentation volume and degree of flocculation nearing 1. This was due to the presence of anti caking agents or the granule disintegrant added to the formulations. Also formulation with Acacia (3% and 1.5%) showed good redispersibility.
Keywords: Ambroxol HCl, Azithromycin, Xanthum gum.

Introduction and Experimental

Although conventional oral suspension can be administered immediately. There is an important category of suspension that requires mixing prior to administration. These are dry mixtures that require the addition of water at the time of dispensing .the reconstituted system is the formulation of choice when the drug stability is a major concern. After reconstitution, these systems have a short but acceptable life if stored at refrigerator temperatures.[1,2]
Reconstitutable oral systems show adequate chemical stability of the drug during shelf life, avoids the physical stability problems related to solubility, pH, and incompatibilities with other ingredients and also reduce the weight of the final product because the aqueous vehicle is absent and consequently the transportation expenses may be reduced.[3]
The objective of the present study was to develop dry suspensions for reconstitution of Azithromycin and Ambroxol HCl using powder blends techniques. The study also aimed at determining the effects of these conditions in the formation of oral reconstitutable suspension and to evaluate different types and concentrations of suspending agents required for effective physical stability of the formulations. The prepared suspensions were evaluated for flow properties, rheological and sedimentation behavior.[4,5,6,9]

Materials and Methods[10-19]

Azithromycin was obtained as gift sample from IPCA Labs, Ratlam and Ambroxol HCl was obtained as gift sample from Schon Pharma, Indore (India) Acacia, Sodium CMC, Xanthum gum and other excipients used in the processing of manufacture of the suspensions, were of IP. All the other reagents or solvents used were of analytical grade.

Formulation of oral reconstitutable suspension:
Powder blend of Azithromycin and Ambroxol HCl was prepared using suspending agents, sweetener, preservative, flavourant, anti-caking agent and granule disintegrant by conventional technique. All the ingredients were passed through 200# before mixing.wet granulation was the usual process. The drug was dry blended with the other ingredients. The solid ingredients were blended and massed using isopropyl alcohol. The wet mass was formed into granules using 18#.the formed granules were dried in the oven and passed through 20# after drying (Table 1).

Evaluation

Particle size:
The oral reconstitutable suspensions were evaluated, average particle size of the formulation was examined using standard microscopy method average and standard deviations of 100 particles were estimated (Table 3).

Viscosity:
The rheological behavior of the suspension was determined by using Brookfield viscometer (Model - LVDI).

Sedimentation behavior:

1) Redispersibility:
The redispersibility was determined was determined by studying number of strokes to redisperse the formed sediment at the end of 7 days of storage of the formulations (not more than 100 strokes=Redispersibility).

2) Sedimentation Volume Ratio (SVR):
During the seventh day study sedimentation behavior of formulations was studied for sedimentation volume (F) and degree of flocculation (β)

Zeta potential measurement:
The zeta potential was measured in triplicates in multimodal mode. The technique opted was Malvern zetasizer inspection system (Malvern UK) respectively at 25^0C. Prior to the measurement, Suspension was diluted with distilled water and the measurements were taken in triplicate.

Drug content:
One ml of the suspension (25mg) was pipette into 100 ml volumetric flask. 50 ml of 0.1 N HCl was added to this & mixed well for 15 min & volume was made up to 100ml by adding sufficient 0.1 HCl **(Table 4).** The solution was analyzed at 251nm & 301 nm for Ambroxol HCl & Azithromycin respectively.

Table1: Formulation of oral reconstitutable suspension

Formulations	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
Azithromycin	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Ambroxol HCl	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Acacia	10.0	5.0	-	-	-	-	-	-
Sodium CMC	-	-	6.0	3.0	-	-	-	-
Tragacanth	-	-	-	-	5.0	2.5	-	-
Xanthum gum	-	-	-	-	-	-	5.0	2.5
SSG	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Sucrose	45.8	50.8	49.8	52.8	50.8	53.3	54.8	55.3
Sodium benzoate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Banana Flavour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified water q.s to	100	100	100	100	100	100	100	100

Table 2: Evaluation data on flow properties of reconstitutable oral suspension

Formulation	Angle of repose	Bulk Density (g/cm^3)	Tap Density (g/cm^3)
F1	8.6±0.01	0.45±0.01	0.46±0.01
F2	4.2±0.01	0.43±0.05	0.52±0.01
F3	7.6±0.11	0.47±0.12	0.55±0.11
F4	4.4±0.01	0.45±0.01	0.55±0.01
F5	9.2±0.01	0.48±0.01	0.55±0.12
F6	6.4±0.01	0.46±0.01	0.45±0.01
F7	10.4±0.11	0.43±0.01	0.47±0.04
F8	9.5±0.01	0.45±0.01	0.44±0.11

Table 3: Evaluation of reconstitutable oral suspension

Formulation	Avg. particle size (µm)	Viscosity (cps)	Redispersibility (No. of strokes)	Sedimentation volume	
				F	B
F1	20.5	600±0.12	6	0.39	0.78
F2	22.5	553±0.11	8	0.45	0.84
F3	21.8	502±0.10	7	0.37	0.68
F4	22.3	412±0.15	6	0.39	0.76
F5	21.3	500±0.24	8	0.38	0.79
F6	23.0	400±0.12	5	0.41	0.88
F7	21.1	600±0.15	6	0.89	0.89
F8	22.3	505±0.14	6	0.98	0.98

Figure 1: Zeta potential of formulation F1

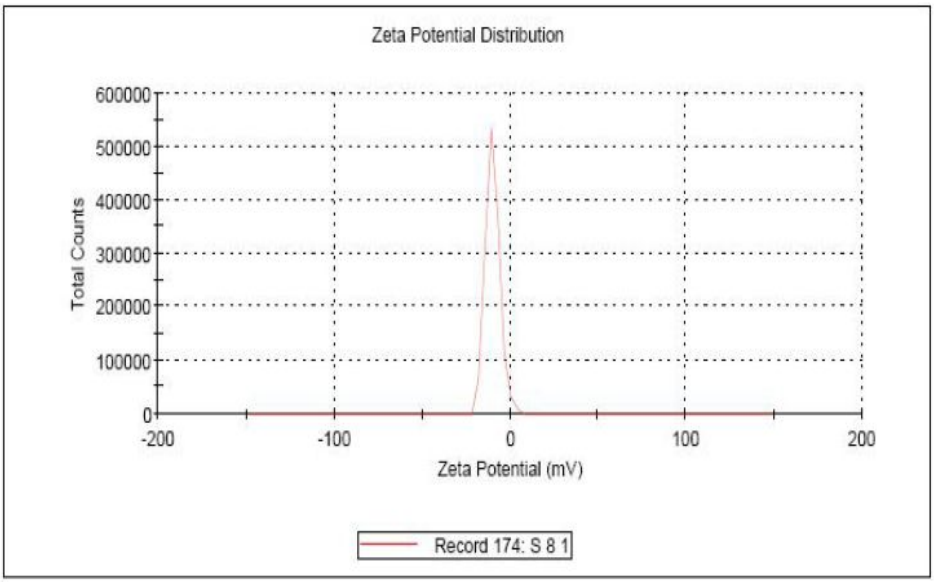

Figure 2: Zeta potential of formulation F2

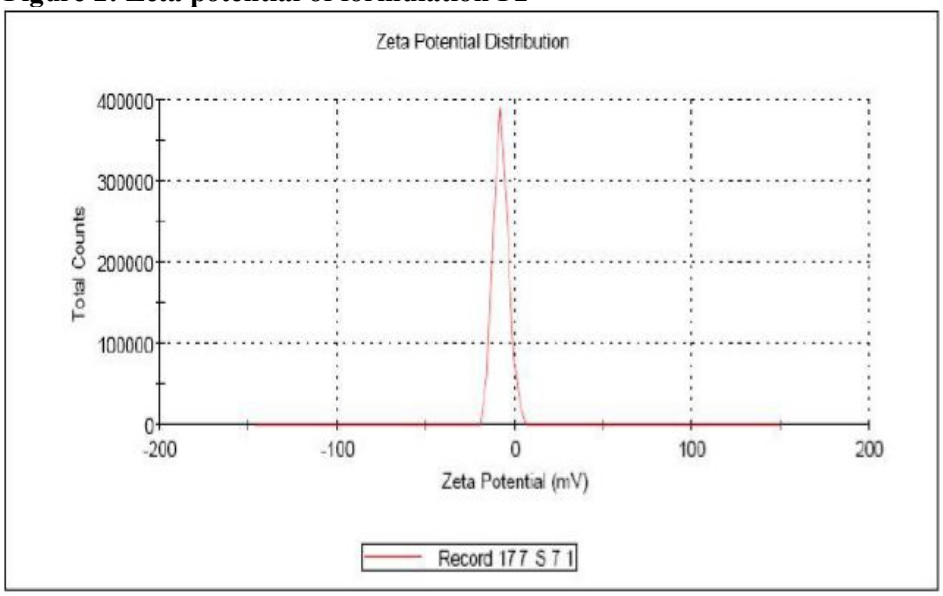

Figure 3: Zeta potential of formulation F7

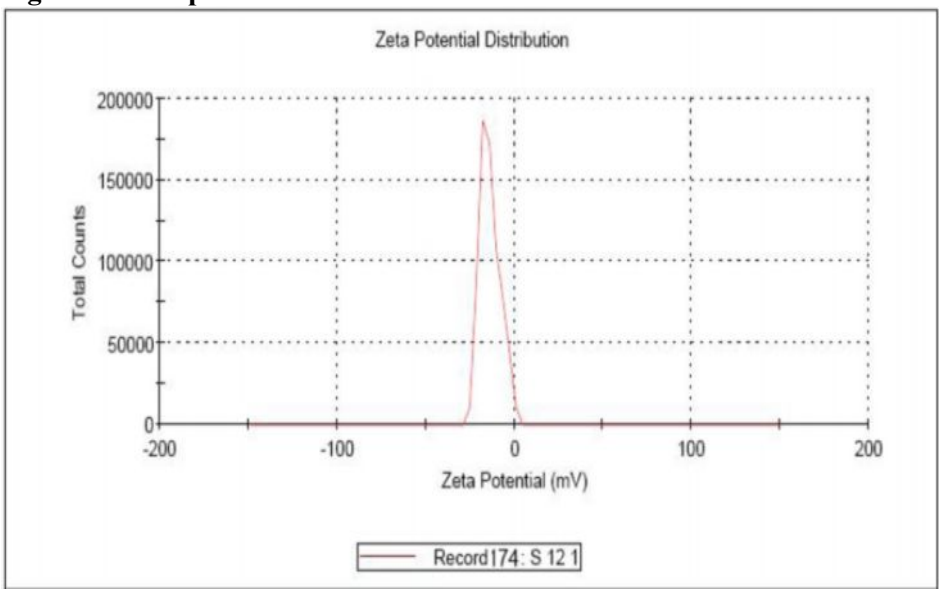

Figure 4: Zeta potential of formulation F8

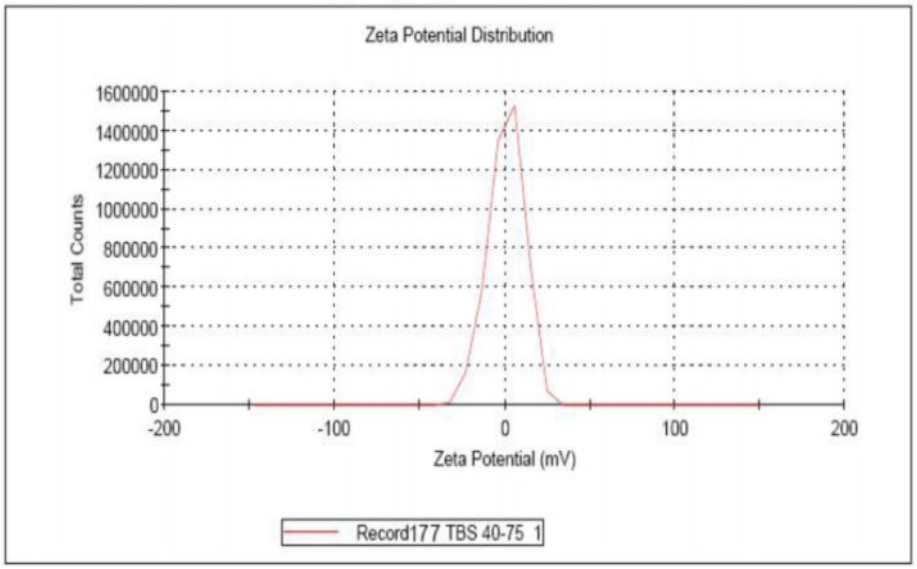

Table 4: Evaluation of oral reconstitutable suspension

Formulation	Zeta potential (mV)	Drug content (%)	
		Azithromycin	Ambroxol HCl
F1	-10.01	97.09±1.05	97.27±1.15
F2	-8.06	98.95±0.70	97.19±0.70
F3	-13.90	99.50±0.22	98.60±0.32
F4	.718	99.96±0.82	98.81±0.51

***In vitro* release study:**

The *in vitro* release profile of the selected batch of reconstituted suspension was obtained by using USP type II dissolution apparatus. 5ml of reconstituted suspension equivalent to about 200 mg of Azithromycin & 30 mg of Ambroxol HCl was accurately weighed and put into 500 ml of 0.1 N HCl (37°±0.5° C) and stirred at 50 rpm(Figure 5,6). Aliquots were taken at predetermined intervals and analyzed spectrophotometrically at 251nm & 301 nm for Ambroxol HCl & Azithromycin respectively.

Stability study:
The reconstitutable suspension were stored in air tight amber coloured glass bottles for 36 days at 45°C and then reconstituted with distilled water to make up the volume to 60 ml with gentle shaking(Table 5). The reconstituted suspensions were stored at 4°C, 25°C and 45°C for 15 days. The reconstituted suspension stored at various temperatures evaluated after reconstitution and after 7th and 15th day of reconstitution.

Figure 5: *In vitro* release of Azithromycin

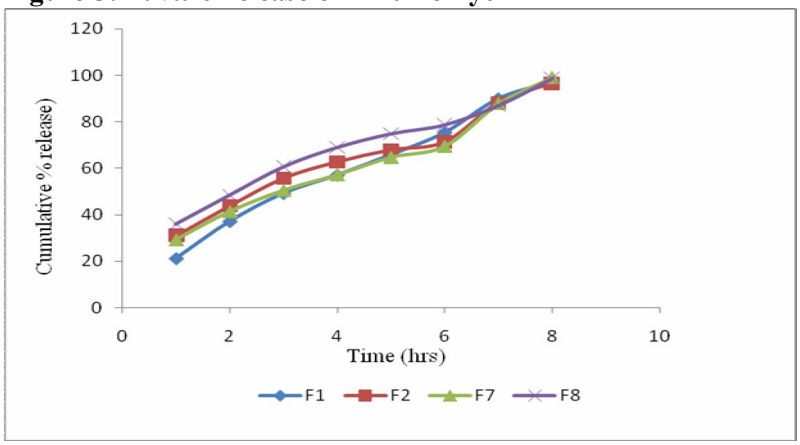

Figure 6: *In vitro* release of Ambroxol HCl

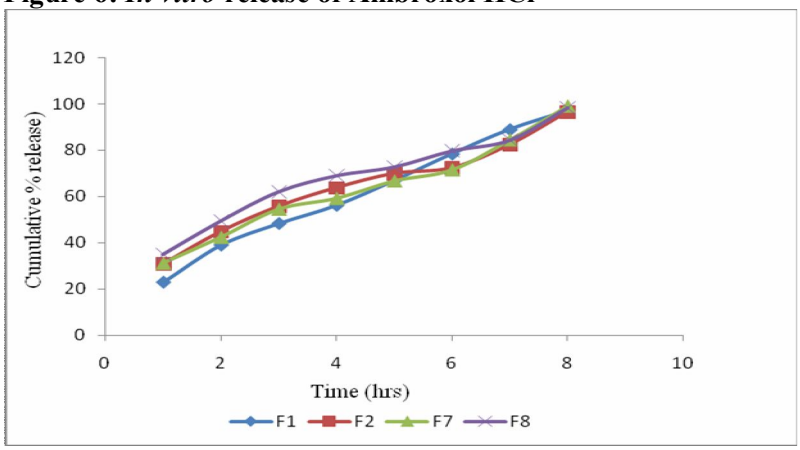

Table 5: Stability study of various formulations

Formulation F1						
		Day1	Day6	Day12	Day24	Day36
Sedimentation rate	F	0.39	0.37	0.34	0.28	0.22
	β	0.78	0.71	0.69	0.61	0.51
Viscosity		601±0.12	500±0.15	453±0.20	410±0.34	320±0.10
Formulation F2						
Sedimentation rate	F	0.45	0.41	0.37	0.32	0.26
	β	0.84	0.82	0.79	0.67	0.47
Viscosity		553±0.11	451±0.12	410±0.12	390±0.12	362±0.12
Formulation F7						
Sedimentation rate	F	0.89	0.87	0.81	0.78	0.71
	β	0.82	0.83	0.80	0.76	0.67
Viscosity		600±0.15	571±0.13	530±0.01	514±0.12	470±0.11
Formulation F8						
Sedimentation rate	F	0.98	0.92	0.88	0.63	0.61
	β	0.98	0.87	0.78	0.67	0.62
Viscosity		505±0.14	486±0.15	440±0.11	412±0.12	350±0.15

Result & Discussion

All formulations showed excellent flow properties. Acacia and Sodium CMC showed similar flow properties (Table 2) formulation with Sodium CMC (6% and 3%) and Tragacanth (5% and 2.5%) gave very stiff suspensions on reconstitution and hence did not show dispersion. These formulations were therefore not evaluated for sedimentation and rheological behaviour. Formulation with Xanthum gum (5% and 2.5%) showed excellent sedimentation volume and degree of flocculation nearing 1.

In conclusion a study was carried out to determine the effects of different conditions in the formation of oral reconstitutable suspension and to evaluate different types and concentration of suspending agent required for effective physical stability of the formulations. In the given concentrations of the suspending agents Acacia, Xanthum gum and SSG shows excellent suspending properties after reconstitution at the same time, in the given concentration, Tragacanth, Sodium CMC show excellent flow properties. The study helped to evaluate a wide range and concentrations of suspending agents as anti- caking agents and super disintegrants for optimization of oral reconstitutable suspension. Oral reconstitutable systems are thus cost effective along with simple technology for large scale manufacturing.

References

1. Ofner CM, Schnaare RL, and Schwartz JB "Reconstitutable oral suspension",FMC Corporation, NJ,1984,P.243-259.
2. Howard C.A., 1981, Introduction of pharmaceutical dosage forms (Lea and Febiger, Philadelphia, PA), pp.139-166.
3. Lieberman H.A, Rieger M.M, Banker G.S.1994 Pharmaceutical dosage forms and disperse system (New York: Marcel dekkar Inc.).
4. Banker G.S.Rhodes C.T.1979, Dispersed system (New York Marcel Dekker,INC)72, 345-346.
5. Nutan MTH, Reddy IK, IN; Kulshrestha AK, Singh ON, Wall GM, editors, Pharmaceutical suspensions from formulation development to manufacturing, 1st ed. USA: Springer publication;2010,39-55.
6. Ansel C., Allen L.V., Popovich N.G. Eighth edition "Disperse systems" Pharmaceutical Dosage Forms & Drug Delivery Systems, Lippincott Williams and Wilkins, Philadelphia 2005, 387-389, 398.
7. Bhalerao S.S., Lalla J.k and Rane, M.S., A Study of electrokinetic and stability properties of suspensions of Diltiazem hydrochloride microspheres,Indian Drugs, 389 2001, 464-467.
8. Nutan MTH, Reddy IK Kulshrestha AK, Singh ON, Wall GM, editors, Pharmaceutical suspensions from formulation development to manufacturing, 1st ed. USA: Springer publication;2010, 41-56.
9. Michael J. Fakiewicz "Theory of suspension" pharmaceutical dosage forms:disperse system Vol.I Second edition , revised & expanded Herbert A Lieberman,martin M.Rieger & Gilberts. Banker.1998; 17-52.
10. Swarbrick J, Boylan JC. Encyclopedia of pharmaceutical technology. 3rd ed. Marcel Dekker New York: 2002. (129); 370.
11. Bari S.B,Mahajan B.M and Surana S.J "Resistance to antibiotics " Indian J pharm Educ.Res Jan-Mar 12(b);3-10.
12. Prabakaran L, Bajpai M, and Saini TR. "formulation development and optimization studies of satranidazole oral suspension" J Pharma Res. Vol.4, No.2, April 2005:19-23.
13. Michael J. Fakiewicz "Theory of suspension" pharmaceutical dosage forms:disperse system Vol.I Second edition , revised & expanded Herbert A Lieberman,martin M.Rieger & Gilberts. Banker.1998; 17-52.
14. Martindale, The extra pharmacopoeia. 23rd ed. London: Royal pharmaceutics Society, 1996. P.175-176.
15. The United State Pharmacopoeia. 23rd ed. Easton: Mack Publishing Company; 1995. p.1342.
16. The Indian Pharmacopoeia Vol I, 2007, 758
17. The British Pharmacopoeia Vol I, 1988.105 & 192.
18. Raymond CR, Paul JS, Sian CO, Handbook of pharmaceutical Excipients, 5th ed. London and Washington: The pharmaceutical Press and The American Pharmacist Association; 2006.p124-125,743-747,821-823.
19. Pendarkar NA, Chaple DR. Simultaneous estimation of azithromycin and ambroxol hydrochloride in combined tablet dosage form by multicomponent mode of analysis. Asian J Res Chem. 2010;3(2):296-298.

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